Past, Present and Future of EPA Post-Marketing Adverse Event Surveillance Systems

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Monitoring Consumer Product Safety

- Pre-market Assessment
  - **Basic Science Bench Research on ingredients**
  - **Epidemiologic review of use patterns**
  - **Consumer use/acceptance or R&D placement studies**
  - **"Controlled" clinical trials**
  - **Screening of ingredient combinations, anticipating issues**

Monitoring Consumer Product Safety

- Post-market Assessment
  - **Product vs. ingredient**
  - **Review and assess "uncontrolled,…real life" use**
  - **Intended to confirm pre-determined or assumed safety**

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Study Population Size Necessary to Identify 1, 2, or 3 Cases of a Given Effect Based on its Relative Incidence

AE Frequency	Number of AE Cases		
	1	2	3
1 out of 100	300	480	650
1 out of 200	600	960	1,300
1 out of 1,000	3,000	4,800	6,500
1 out of 2,000	6,000	9,600	13,000
1 out of 10,000	30,000	48,000	65,000

Post-Market/In-Market Surveillance

- What is it????
  - **The processes whereby manufactures, regulators, health professionals, the public at large, and others monitor the performance and experience related to a given products life-cycle in the open market.**

Post-Market Surveillance

What should it accomplish??

- **Helps identify intended *and* unintended use patterns that may potentially contribute to "unintended effects"**
- **Allows assessment of how the product performs by itself or in the presence of other products or substances**
- **Helps insure that effects in "unique" populations are considered when evaluating risk**
- **Engages all stakeholders in a sensitive but specific system of "Signal Detection"**
- **Should also help define a relative "*Safety* profile"**

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Post-Market Surveillance

Why is signal detection important??

Consider the GM Ignition Switch Failure Fiasco

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Office of Inspector General

Audit Report

INADEQUATE DATA AND ANALYSIS UNDERMINE NHTSA'S EFFORTS TO IDENTIFY AND INVESTIGATE VEHICLE SAFETY CONCERNS

National Highway Traffic Safety Administration

Report Number: ST-2015-063
Date Issued: June 18, 2015

The New York Times | http://nyti.ms/1evW85E

BUSINESS DAY

Federal Auditor Finds Broad Failures at N.H.T.S.A.

By DANIELLE IVORY JUNE 19, 2015

Even as evidence poured into the nation's top auto safety agency pointing to dangerous defects in millions of vehicles, regulators repeatedly failed for years to root out problems and hold carmakers accountable, according to a long-awaited internal audit by the Transportation Department.

The bluntly worded report, ordered last year after **General Motors began recalling** 2.6 million cars with a defective ignition switch, paints a bleak portrait of the **National Highway Traffic Safety Administration**, the agency charged with overseeing safety in the auto industry.

The agency had weak management, undertrained staff and insufficient processes in place to properly review safety data submitted by automakers and complaints submitted by drivers, the report by the Transportation Department's inspector general found. Repeatedly, investigators missed opportunities to identify that the ignition switch was prone to turn off, shutting down the engine and disabling systems like power steering and the airbags. At least 114 deaths have been linked to the defect. And the agency's shortcomings extended to other problems as well.

Ultimately, the report said, the agency's systemic failings "deter N.H.T.S.A. from successfully meeting the mandate to help prevent crashes and their attendant costs,

Adverse Event Reporting

- NHTSA & the GM Ignition Switch Issue:
  - Had gone on for over a decade
  - Occurred despite NHTSA mandatory reporting requirements for manufacturer reporting of AEs
  - Issues
    - Lack of standardized reporting, coding of issues, investigation, and action on the part of manufacturers and regulators alike

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Post-Market Surveillance

The Art and Science of "Signal Detection"

Adverse Event Reporting vs. Postmarket Surveillance

- Adverse Event Reporting:
  - Meeting the Letter of the Law(s)
    - Prescriptive process of handling spontaneously reported allegations of product associated injury:
      - RECEIVING
      - DOCUMENTING
      - TABULATING
      - SUBMITTING

Adverse Event Reporting vs. Postmarket Surveillance

- Postmarket Surveillance:
  - Meeting the **Intent** of the Law
    - Performance based process of:
      - Incident investigation: Collecting, Documenting, Categorizing incident details
      - Interpretation/Utilization
      - Analysis for Causation (Association), hypothesis generation
      - Education, corrective action or risk mitigation efforts

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Adverse Event Reporting vs. Postmarket Surveillance

- Postmarket Surviellance:
  - Meeting the **Intent** of various adverse event surveillance initiatives (both legislative and corporate)
    - Performance based process of:
      - Reaching a mutual or shared understanding ,..and acceptance,….of risk with all stake-holders

Adverse Event Possibilities

- A consumer reported using my product and experienced an adverse effect,..is it due to…
  - Inherent product hazard?
  - Manufacturing issue?:
    - Quality control issue that affects product performance and occurring before or after leaving the plant
      - Intentional/accidental
    - Contamination/adulteration after sale
      - Supply chain issue?
      - Malicious event including home-land security issue

Adverse Event Possibilities

- A consumer reported using my product and experienced an adverse effect,..is it due to…
  - Predictable adverse effect based on:
    - Inherent toxicity/hazard profile of one or more of the ingredients (*or contaminants*)
      - Allergy
    - Known interaction potential with:
      - Drugs, food, pre-existing disease or medical condition
      - Other consumer products, etc.

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Adverse Event Possibilities

- A consumer reported using my product and experienced an adverse effect,..is it due to…
  - Unexpected effect
    - Idiosyncratic (simply unknown, unpredictable)
      - Allergy
      - Biologic (gene expression)
    - Other unrecognized "reaction" (direct?)
    - Other unrecognized "interaction"
      - Drugs, food, pre-existing disease or medical condition
      - Other consumer products, etc.
      - Environmental issue

Adverse Event Possibilities

- A consumer reported using my product and experienced an adverse effect,..is it due to…
  - Unanticipated effect secondary to:
    - Unexpected use pattern
    - Labeling issue
    - Intentional “misuse”
    - Intentional “abuse”

Adverse Event Possibilities

- A consumer reported using my product and experienced an adverse effect,..is it due to…
  - NONE OF THE ABOVE!!!

AKA……

"Background Noise"

Adverse Event Possibilities

- Background Noise
  - Concomitant disease
    - Spontaneous disease
    - Exacerbation of existing disease
    - Disease out of remission
  - Direct toxic effect due to something else
  - Mis-identification of the potentially offending substance or product

Adverse Event Possibilities

- Background Noise
  - Herd mentality reporting "I heard it through the grapevine":
    - Twitter chatter, FaceBook, Blogs, other "social media"
    - Friends and relatives
    - Commercial Media outlets
    - Other phantom issues leading to a feeding frenzy
  - None of the above…"it really didn't happen"
    - "Syringe in the Pepsi Can" syndrome

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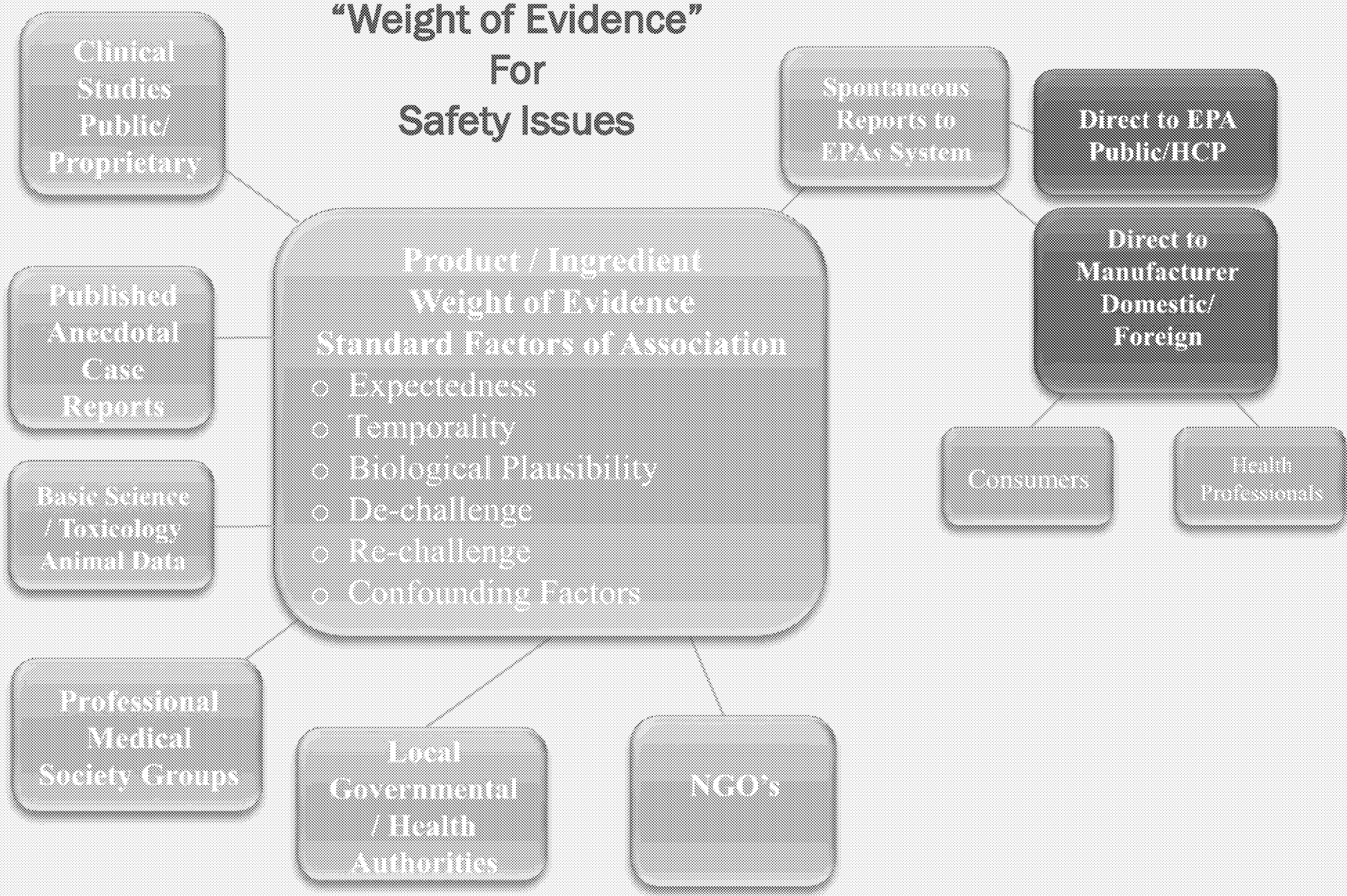
“Not all ‘adverse events’ or ‘adverse event reports’ are created equal”

HHE
"Weight of Evidence"
For
Safety Issues



Adverse Event Surveillance and Reporting Systems

EPA Options for Accessing Adverse Event Information

Sources of Post-Market Product Exposure Information

American Association of Poison Control Centers Annual Report (AAPCC)

- Previously known as TESS DB, recently renamed National Poisoning and Exposure Database (NPDS)
- Annual reports

  "This tool is especially recommended for use by reporters, students, and people looking for high level general statistics"

Sources of Post-Market Product Exposure Information

NPDS Data (From 56 Centers)

- 2.2 million "poison exposure" calls 2014 (representing incident rate of 6.7 incidents/thousand population)
  - Normalized incident rate peaked at 9.7 in 1993
- "exposure" vs. "poisoning" terms are not synonymous but routinely used interchangeably
- Cases are coded using a standardized reporting format and product coding system

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Table 12. Medical Outcome by Reason for Exposure in Human Exposures[a].

	Unintentional		Intentional		Other		Adverse reaction		Unknown		Total	
Outcome	N	%	N	%	N	%	N	%	N	%	N	%
Death	158	0.01	1,064	0.29	10	0.06	81	0.16	246	1.53	1,559	0.07
Death, indirect report	27	0.00	213	0.06	6	0.04	3	0.01	27	0.17	276	0.01
Major effect	2,623	0.15	17,247	4.76	165	1.03	776	1.50	1,315	8.20	22,126	1.02
Minor effect	209,432	12.19	104,936	28.94	2,868	17.90	12,024	23.28	2,569	16.02	331,829	15.33
Moderate effect	42,570	2.48	94,810	26.14	1,185	7.40	7,452	14.43	3,892	24.27	149,909	6.92
No effect	328,561	19.12	61,323	16.91	1,750	10.92	1,445	2.80	1,269	7.91	394,348	18.21
No follow-up, nontoxic	268,396	15.62	4,178	1.15	1,190	7.43	1,039	2.01	283	1.76	275,086	12.71
No follow-up, minimal toxicity	787,066	45.79	33,176	9.15	6,175	38.54	17,511	33.90	1,909	11.90	845,837	39.07
No follow-up, potentially toxic	45,067	2.62	37,928	10.46	1,549	9.67	3,526	6.83	3,038	18.94	91,108	4.21
Unrelated effect	34,868	2.03	7,786	2.15	1,126	7.03	7,794	15.09	1,490	9.29	53,064	2.45
Total	**1,718,768**	**100.00**	**362,661**	**100.00**	**16,024**	**100.00**	**51,651**	**100.00**	**16,038**	**100.00**	**2,165,142**	**100.00**

[a]Total number of cases where Death was an outcome (1,559+276) is greater than the number of fatalities (1,173) judged to be exposure-related (relative contribution to fatality of 1-Undoubtedly responsible, 2-Probably responsible, or 3-Contributory).

23.35%

Table 22A. Demographic profile of SINGLE SUBSTANCE Nonpharmaceuticals exposure cases by generic category.

			Age							Reason					Outcome				
	No. of Case Mentions	No. of Single Exposures	<=5	6-12	13-19	>=20	Unknown Child	Unknown Adult	Unknown Age	Unint	Int	Other	Adv Rxn	Treated in Health Care Facility	None	Minor	Moderate	Major	Death
Organophosphate Insecticides Alone	2,255	2,180	596	132	70	1,124	13	214	31	2,010	72	31	52	573	478	473	109	20	3
Organophosphate Insecticides in Combination with Carbamate Insecticides	40	39	10	5	0	18	0	6	0	33	2	2	2	6	10	6	1	0	0
Organophosphate Insecticides in Combination with Non-Carbamate Insecticides	506	474	86	22	23	276	0	65	2	446	12	4	9	104	71	96	26	3	0
Other Types of Insecticide	9,278	8,729	4,063	367	205	3,252	20	713	109	8,425	95	47	143	773	1,585	802	93	6	1
Pyrethrins	5,667	5,304	1,706	444	226	2,362	20	478	68	4,842	148	31	254	944	723	1,202	219	1	0
Pyrethroids	22,695	21,490	5,388	1,168	875	11,619	54	2,167	279	19,989	537	201	697	3,344	3,059	5,121	633	25	1

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Organophosphate Insecticides in Combination with Carbamate Insecticides	40	39	10	5	0	18	0	6	0	33	2	2	2	6	10	6	1	0	0
Organophosphate Insecticides in Combination with Non-Carbamate Insecticides	506	474	86	22	23	276	0	65	2	446	12	4	9	104	71	96	26	3	0
Other Types of Insecticide	9,275	8,729	4,063	367	205	3,252	20	713	109	8,425	95	47	143	773	1,585	802	93	6	1
Pyrethrins	5,667	5,304	1,706	444	226	2,362	20	478	68	4,842	148	31	254	944	723	1,202	219	1	0
Pyrethroids	22,695	21,490	5,388	1,108	875	11,619	54	2,167	279	19,989	537	201	697	3,344	3,059	5,121	633	25	1

26,794

685

6,323
24.5%

852
3.2%

26
.09%

1

26.8%

Table 6A. Reason for Human Exposure Cases.

Reason	N	% Human exposures
Unintentional		
Unintentional – General	1,164,029	53.8
Unintentional – Therapeutic error	271,737	12.6
Unintentional – Misuse	125,086	5.8
Unintentional – Environmental	58,586	2.7
Unintentional – Bite/sting	49,914	2.3
Unintentional – Occupational	26,880	1.2
Unintentional – Food poisoning	19,343	0.9
Unintentional – Unknown	3,193	0.1
Subtotal	**1,718,768**	**79.4**
Intentional		
Intentional – Suspected suicide	241,804	11.2
Intentional – Misuse	54,679	2.5
Intentional – Abuse	46,727	2.2
Intentional – Unknown	19,451	0.9
Subtotal	**362,661**	**16.7**
Adverse Reaction		
Adverse reaction – Drug	36,542	1.7
Adverse reaction – Other	10,055	0.5
Adverse reaction – Food	5,054	0.2
Subtotal	**51,651**	**2.4**
Unknown		
Unknown reason	16,038	0.7
Subtotal	**16,038**	**0.7**
Other		
Other – Contamination/tampering	7,472	0.3
Other – Malicious	7,051	0.3
Other – Withdrawal	1,501	0.1
Subtotal	**16,024**	**0.7**
Total	**2,165,142**	**100.0**

NPDS Data
Frequency ≠ Severity

- NPDS data mirror product and substance availability, market share, and accessibility in the home
  - **NPDS "exposures" are often not adverse events**
    - **~76% of human exposures reported to NPDS have no adverse clinical effects**
  - **Exposure frequency does not correlate with severity for the 914 NPDS substance categories**

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AAPCC "NPDS" Strenghts/Limitations

- Strengths
  - Basic set of data elements collected on every case
  - Provides a good overall picture of the "marketplace" regarding "Toxic or perceived Toxic" exposures and
  - Is quite "sensitive" vs. "specific"

AAPCC "NPDS" Strengths/Limitations

- Limitations
  - Not designed to be a pharmacovigilance (PV) system
  - Does not integrate with typical PV systems
    - Clinical effects and treatment rendered descriptors were developed for the PC environment
    - Software used by participating centers not typically validated as in other PV systems (eg. FDA Part 11 compliance)

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AAPCC "NPDS" Strengths/Limitations

- Limitations
  - Not as sensitive for adverse reaction types of exposures vs. acute unintentional exposures
  - Product codes/coding limitations
  - NO DENOMINATOR FOR NORMALIZATION OF INCIDENCE RATES

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AAPCC "NPDS" Strengths/Limitations

- Limitations
  - AAPCC Disclaimer consistent with other spontaneously reported adverse event systems

"Case records in this database are from self-reported calls: they reflect only information provided when the public or healthcare professionals report an actual or potential exposure to a substance (e.g., an ingestion, inhalation, or topical exposure, etc.) or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers."

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Sources of Post-Market Product Exposure Information

CDC/NIOSH-LED SENSOR- PESTICIDES SYSTEM

- Known as the "*Sentinel Event Notification System for Occupational Risks*"
  - Focused on occupational exposures
  - Relies on data from multiple states

California's Pesticide Illness Surveillance Program (PISP)

Sources of Post-Market Product Exposure Information

National Pesticide Information Center (NPIC)

- Designed to provide objective, science-based information about pesticides
  - Not designed as an adverse event reporting portal, but…..
  - Provides links for reporting options, eg, "Acute poisoning:" Poison Control, Worker Safety: State Regulatory Agencies, Product specific support: Manufacturer surveillance systems

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Company Sponsored Adverse Incident Surveillance Systems:

- Genesis of Service
  - Meeting "consumers expectations" of the manufacturer as being the most knowledgeable and "*responsible*" regarding product safety and performance
  - Complementary,… but distinct from Public Poison Center or other incident surveillance systems with opportunity for consumer and manufacture to cooperate in identifying, mitigating or otherwise resolving product issues

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Company Sponsored Adverse Incident Surveillance Systems

- Focus is often more targeted allowing for:
  - Opportunity to triage/coordinate with customer service
  - Access to detailed records, full narrative reports and opportunity for ongoing "real-time" incident communication and incident investigation
  - Meet regulatory requirements "mandatory AE reporting"
  - Focused/specialized data collection, tabulation, *assessments*,…and analysis

Adverse Event Surveillance and Reporting Systems

- EPA:
  - Past:
    - Pre-September 19, 1997 Adverse Event Reporting
      - Required manufacturer reporting of:
        - » Series of 3 or more adverse events
        - » Incidents involving a pesticide exposure resulting in adverse effects determined to be "caused" by the exposure
  - Present (version 1):
    - Post-September 19, 1997 to present
      - Required manufacturer reporting of "ALL" allegations of AE
      - Utilization of Single incident reports for "Serious/Significant" AEs
      - Aggregation of minor AEs and all domestic animal events by "*clinical effects*" per incident

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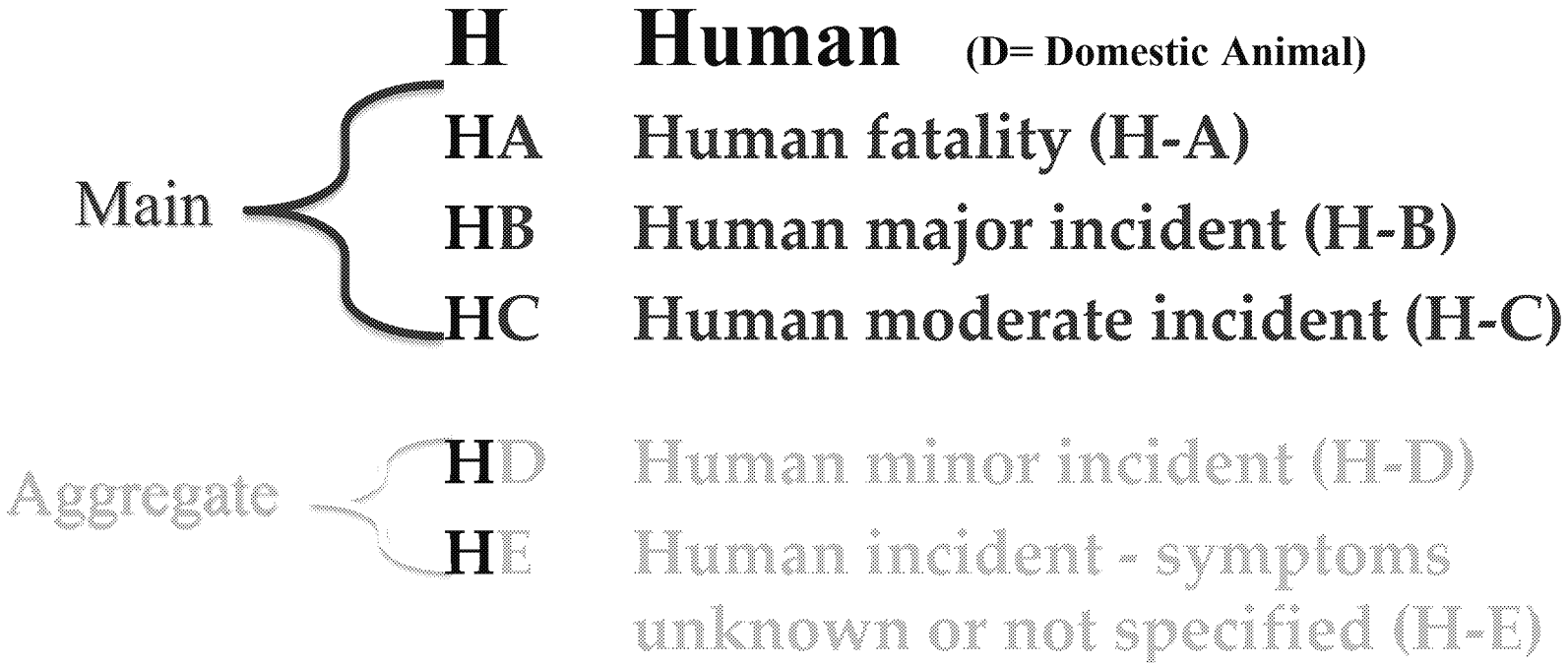
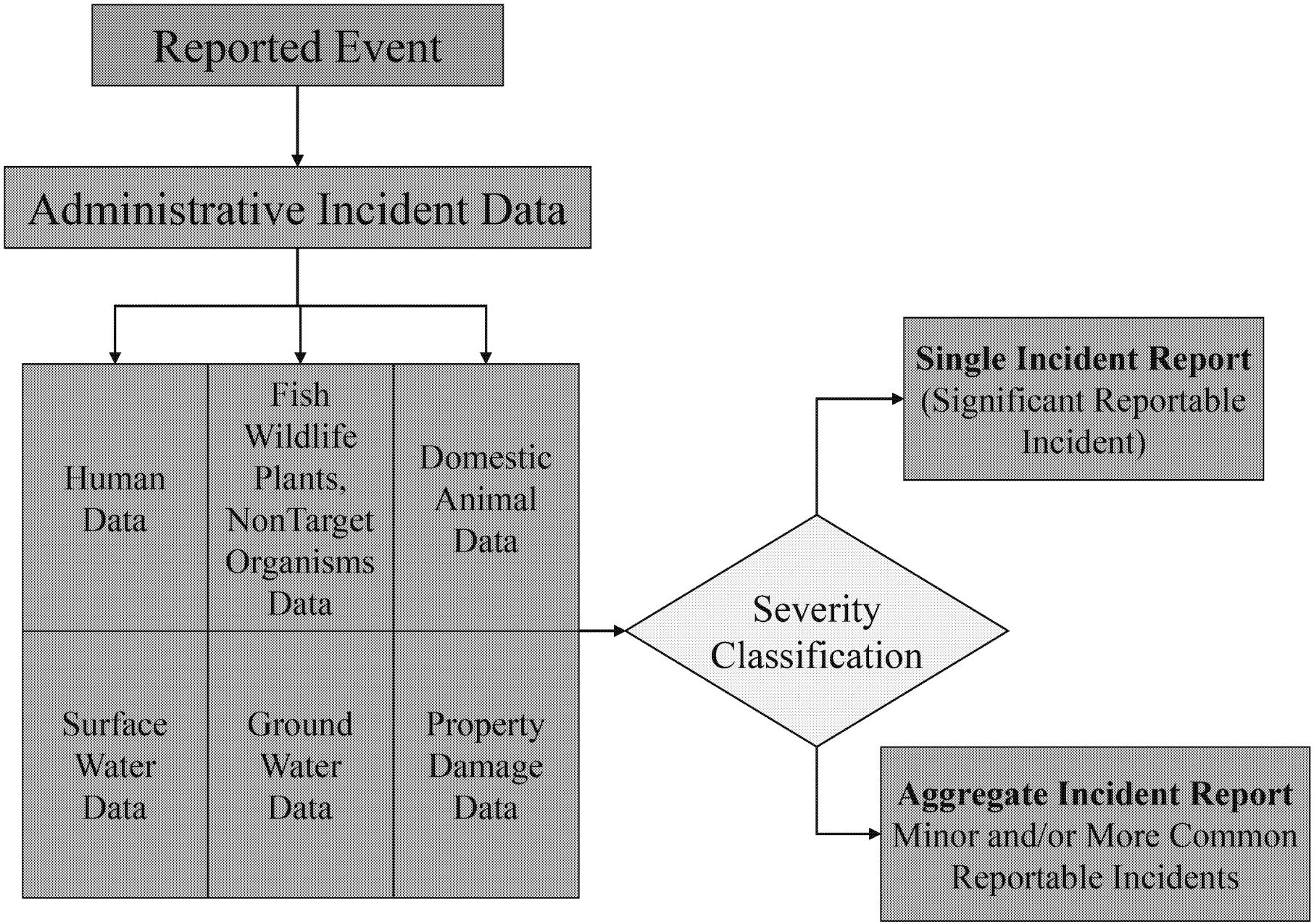
IDS Human Severity Codes*

Main IDS & Aggregate IDS both contain information on incident severity



*codes defined in 40 CFR 159.184 (c) (5) (i)

6(a)(2) Incident Reporting Process



Adverse Event Surveillance and Reporting Systems

- EPA:
  - Present (version 2):
    - Conditional Registrations Part 1
      - Implemented in 2010 requiring manufacturers to collect, analyze and report additional AE data elements beyond typical 6(a)(2) data for conditionally registered products

Part 1: Enhanced Aggregate Reporting

Enhanced Surveillance for Conditionally Registered Products

The following is a list of information that must be included in the quarterly reports for each incident:

a. EPA Registration Number
b. Product Name (brand name)
c. Lot Number
d. Where Purchased: Internet, Store, Veterinarian
e. Active Ingredient(s)
f. Weight Range for Product
g. Date on which incident occurred (mm/dd/yyyy).
h. State in which the incident occurred (standard 2 letter abbreviation).
i. Registrant Case Number
j. Species: Dog, Cat, Other (specify)
k. Breed: (as reported by pet owner)
l. Age: Months or Years
m. Sex: Male, Female
n. Weight: Pounds
o. Primary Route of Exposure: Dermal, Oral, Other Animal, Inhalation, Other
p. Body System: Neurological, Dermatological, GI, Respiratory, Ocular, Other
q. Major Signs: Separate Column for Each Sign, Using Standard Terminology
r. Time to Onset: Hours, Days
s. Treated By Veterinarian: Yes or No
t. First Time Product Used: Yes or No
u. Misuse: Use on Incorrect Species, Overdose, Too Frequent Dosing, Other (describe)
v. Any Known Precondition
w. EPA Severity Code: Death, Major, Moderate, Minor
x. Outcome: Died, Recovered, Still Being Treated, Unknown

Adverse Event Surveillance and Reporting Systems

- EPA:
  - Present (version 2):
    - Conditional Registrations Part 1
      - Implemented in 2010 requiring manufacturers to collect, analyze and report additional AE data elements beyond typical 6(a)(2) data for conditionally registered products
    - Conditional Registrations Part 2
      - Spot on Pilot: Further enhancement of data elements for spot on products subject to conditional registration utilizing new coding requirements including VedDra/MedDra dictionary coding

Current EPA IDS

- Key characteristics of underlying dataset:
  - Virtually all EPA IDS incident data is based on spontaneously reported AEs
  - Vast majority of AEs come directly from the public as compared to other incident data systems (FDA prescription pharmaceuticals) that are based on AEs reported by treating clinicians
  - No confirmation, corroboration or verification that the event, as reported, actually occurred
  - For all reported incidents, assuming all reported details are accurately represented, there is no standardized, systematic "assessment" completed using standard factors of association to ascertain strength of association between reported exposure and reported clinical effects

Current EPA IDS

- Key characteristics of underlying dataset:
  - Each subset of data reported by a given manufacturer has inherent attributes that distinguishes it from data received and reported by other manufacturers
    - Reporting portals, accessibility, availability of trained PV personnel for incident data intake, documentation software, categorization of incident details, reporting enhancers (rebates, money back guarantees/refunds), social media footprint,

Current EPA IDS

- Assuming dataset has high integrity
  - Availability of standardized coding nomenclature?
    - Coding of outcomes
    - Disposition and treatment sites/referrals
    - Coding of clinical effects?
      - » Currently multiple terms to code clinical effects: eg. Vomit, regurgitate, throw-up, emesis, upchuck, puke
        vs.
        implementing VedDra/MedDra terminology requiring significant PV modification, expense and time

Current EPA IDS

- Assuming dataset has high integrity
  - Availability of standardized coding nomenclature?
    - Coding of routine data fields with new standardized categories
      - » Reason for exposure
      - » Route (dermal, ingestion, "animal to animal"….etc.)
      - » Age groups
      - » Acuity/Duration
      - » Treatments/therapies
      - » Animal vs. Human data field descriptors
      - » Product identifiers
      - » Pre-existing diseases and coding of each

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Current EPA IDS

- Assuming dataset has high integrity
  - Analysis
    - » ROR modeling for signal detection (adapted from the UK ADR experience)*
  - Role of incident characterization in evaluating "causal links" and association integrity scoring
    - Expectedness
    - Including "relative incidence rates"
    - Temporality
    - Biologic plausibility
    - De-challenge
    - Re-challenge
    - Confounding variables

**Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports.* Pharmacoepidemiology and Drug Safety 2001; 10:483-486

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Future of EPAs IDS

- Common Ground and Industry Collaborations:
  - There is a need for a robust EPA product surveillance system to insure the safe and effective use of EPA regulated products
  - The current 6(a)(2) system is in need of updating and enhancement
  - Standardization of data collection, nomenclature, categorization of incidents is a desirable outcome
  - Harmonization with other incident databases is also desirable
  - Best practices for data analysis is vital and collaboration between HED staff and industry scientists will likely yield the best outcomes

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Future of EPAs IDS

- Remaining Issues:
  - System enhancement and design changes take time
    - VICH GL 30 design and implementation took 9 years
  - Any change made in one area of a corporate database has a huge ripple effect across all data fields for all AEs
  - Although standardization of data collection, nomenclature and categorization of incidents is highly desirable, it is also very expensive:
    - IT support
    - Database purchases for VedDra/MedDra dictionary coding
    - Staff training
  - Data Analysis concerns:
    - Independent of any data base and coding enhancements, the underlying data has significant limitations. How can these limitations be contextualized to decrease inappropriate reliance on "signals" as confirmation of risk

Thank you!

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